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A Case of Nonalcoholic Steatohepatitis in Central Precocious Puberty Aggravated by Gonadotropin-releasing Hormone Analog

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Abstract: We report the case of a girl with central precocious puberty (CPP) and nonalcoholic steatohepatitis (NASH) aggravated by gonadotropin-releasing hormone analog (GnRHa). She was diagnosed with CCP and began treatment with GnRHa at the age of 8 years and 9 months. She already had mild liver dysfunction and was obese at that time; however, liver dysfunction was aggravated during GnRHa initiation. Her liver dysfunction improved after the discontinuation of GnRHa. Liver biopsy was performed twice during GnRHa initiation and findings suggested NASH. In this case, NASH may have been aggravated by the mechanism of estrogen suppression by GnRHa besides obesity. In conclusion, NASH should be ruled out in obese CPP patients with abnormal liver function before starting GnRHa therapy. CPP patients treated with GnRHa require close examination for the early diagnosis of NASH or its progression.

Key Words: nonalcoholic steatohepatitis, central precocious puberty, gonadotropin-releasing hormone analog, liver dysfunction, obese

Nonalcoholic steatohepatitis (NASH) is a fatty liver disease with histopathological changes similar to those observed in cases of alcohol-induced liver injury without a history of alcohol intake. Although many causes of NASH aggravation have been reported, there are no previous reports of NASH due to gonadotropin-releasing hormone analog (GnRHa) treatment for central precocious puberty (CPP). We report the case of a girl with CPP and NASH aggravated by GnRHa.

CASE REPORT

A 9-year and 11-month-old girl was admitted to our hospital for liver dysfunction. She had a history of low birth weight (2402 g) but no abnormal development. However, she showed breast budding at the age of 6 years and 8 months. Her bone age was 11 years and 1 month when she was 8 years and 7 months old. The gonadotropin-releasing hormone load test showed a peak luteinizing hormone value of 11.0 mIU/mL. The peak luteinizing and follicle stimulating hormone ratio was 1.3. These findings suggested CPP. Magnetic resonance imaging of the pituitary gland and abdominal ultrasonography did not detect neoplastic lesions. She was diagnosed with CCP and began treatment with GnRHa (leuprorelin acetate, 30 μg/kg) at the age of 8 years and 9 months.

At the time of GnRHa treatment initiation, serum alanine aminotransferase (ALT) was slightly elevated (71 U/L), and abdominal ultrasonography revealed a moderate fatty liver. Her body mass index (BMI) was 22.9 kg/m^2, which exceeded the 95th percentile. ALT levels increased to 315 U/L after starting GnRHa treatment. GnRHa was discontinued due to aggravated liver function, and ALT levels decreased to 153 U/L. However, GnRHa treatment was still needed for CPP; so treatment was restarted after 3 months. Her liver function was aggravated again (ALT, 372 U/L). Antinuclear antibody titer increased to 1:640; however, IgG levels were normal. Tests for Hepatitis B, Hepatitis C, Epstein-Barr virus, and cytomegalovirus were negative. Serum copper and ceruloplasmin levels were normal. An ultrasound-guided needle biopsy of the liver showed moderate steatosis, ballooning of hepatocytes, and pericellular fibrosis extending from the central vein (Fig. 1); however, the portal region could not be evaluated (the portal area was not included). She was diagnosed with NASH (Matteoni classification, Type 4; Brunt's grade 2 and stage 2) with a nonalcoholic fatty liver disease activity score of 5. She was treated with an oral vitamin E preparation (tocopherol acetate, 400 mg/day), restrictive diet, and exercise, but her BMI remained unchanged and liver function did not improve.

A second liver biopsy was performed when the patient was 12 years and 5 months old and showed no change (Fig. 2). At the age of 12 years and 8 months, she completed treatment for CPP, and her liver function improved (Fig. 3).

DISCUSSION

NASH involves necrosis, fibrosis, and fat deposition in the liver. In some cases, it may progress to cirrhosis and hepatocellular carcinoma (1). NASH was first reported in children in 1983 (2), and obesity was found to be the most important cause of NASH in children (3).

This patient was obese and had liver dysfunction before starting GnRHa. GnRHa treatment for CPP reportedly has no effect on body weight, blood glucose, and blood lipids (4). In this case, liver function deteriorated although there were no changes in BMI, blood glucose, and blood lipid levels. This suggests that GnRHa can exacerbate NASH. In the literature, estrogen deficiency accelerated NASH progression in ovariectomized mice fed a high-fat and high-cholesterol diet due to increased hepatic macrophage infiltration (5). Therefore, the risk of developing NASH and disease progression are high in postmenopausal women (5,6). Furthermore, tamoxifen, an estrogen antagonist, has been reported as a cause of drug-induced NASH. Tamoxifen may lead to increased fat accumulation in the liver by disturbing fatty acid β-oxidation in hepatocytes, a known estrogen-dependent action. Therefore, ω-oxidation may take place as a compensatory reaction and produce dicarboxylic acid, a mitochondrial toxin, which results in damage to the mitochondria of hepatocytes and, eventually, NASH (7). The aggravation of NASH by GnRHa may be based on a similar mechanism of estrogen suppression.

NASH has a high prevalence in patients with diabetes, cardiovascular disease, and inflammatory bowel disease because it is a disease that continues to adulthood (1). In some children, NASH progresses rapidly during childhood (8). Therefore, early diagnosis and treatment

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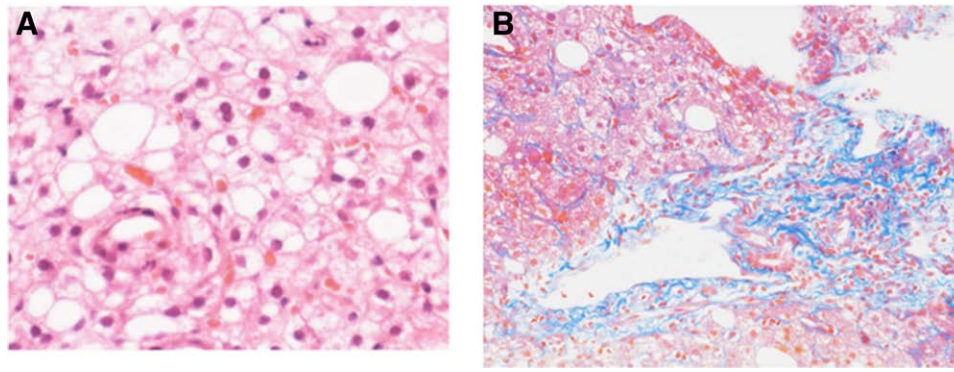

FIGURE 1. Initial liver biopsy specimen. A, Hematoxylin-eosin stain (original magnification ×100). B, Azan stain.

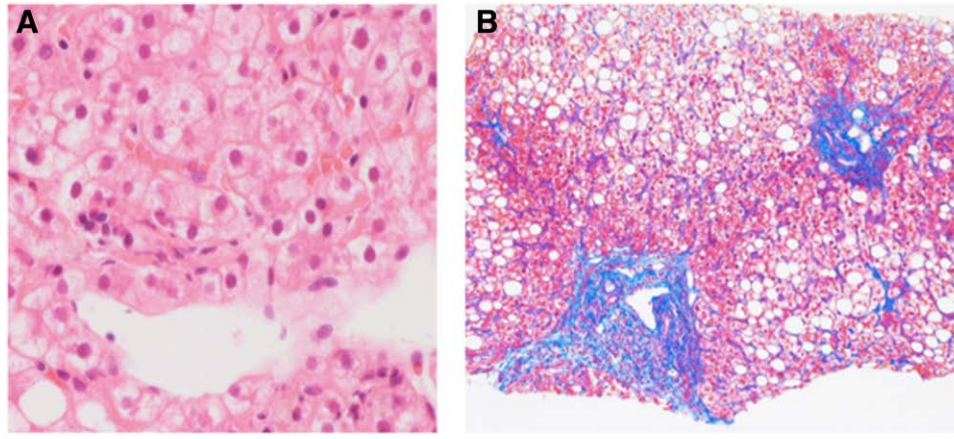

FIGURE 2. Second liver biopsy specimen. A, Hematoxylin-eosin stain (original magnification ×100). B, Azan stain.

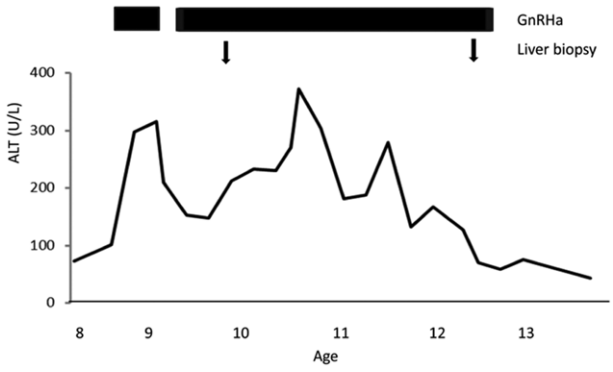

FIGURE 3. Trend of ALT in this case. ALT indicates alanine aminotransferase; GnRHa, gonadotropin-releasing hormone analog.

are needed. In this patient, although liver dysfunction improved after stopping GnRHa therapy, liver biopsy showed unchanged NASH findings. This patient requires a strict long-term follow-up.

In conclusion, NASH should be ruled out in obese CPP patients with abnormal liver function before starting GnRHa therapy. CPP patients treated with GnRHa require close examination for the early diagnosis of NASH or its progression.

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